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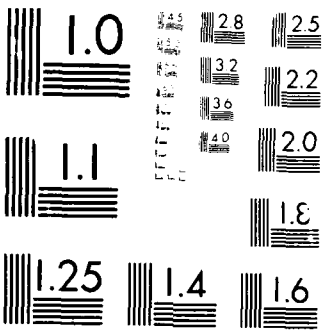
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Interaction between Lung Mechanics and Gas Exchange by Low Volume High Frequency Pulmonary Ventilation in Patients with Respiratory Failure

Final Report

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During the tenure of this contract, research was conducted both in patient volunteers and in hardware models. The patient studies led to the realization that dynamic hyperinflation of the lungs could commonly occur during high frequency ventilation and physiological experiments were conducted to determine the mechanisms responsible for this. The modelling studies (at MIT) first established the nature of the pressure-flow relationships which existed during high-frequency ventilation in a rigid tube model with lung-like geometry. The [illegible] between pressure and flow and gas transport was then established by measuring, in a similar model, the transport coefficients under circumstances dynamically similar to high frequency ventilation. Finally, since the patient studies suggested that expiratory flow limitation may be of critical value in understanding the dynamic hyperinflation observed in patient studies, fluid dynamic modelling of flows [illegible]

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19. (continued) limitation was performed in order to better understand the physical factors influencing dynamic airway collapse. In this report, we shall summarize the work completed in each area, the details of which may be found in the appropriate annual reports.

FOREWORD

For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

INTRODUCTION

During the tenure of this contract, research was conducted both in patient volunteers and in hardware models. The patient studies led to the realization that dynamic hyperinflation of the lungs could commonly occur during high frequency ventilation and physiological experiments were conducted to determine the mechanisms responsible for this. The modelling studies (at MIT) first established the nature of the pressure-flow relationships which existed during high frequency ventilation in a rigid tube model with lung-like geometry. The link between pressure and flow and gas transport was then established by measuring, in a similar model, the transport coefficients under circumstances dynamically similar to high frequency ventilation. Finally, since the patient studies suggested that expiratory flow limitation may be of critical value in understanding the dynamic hyperinflation observed in patient studies, fluid dynamic modelling of flow limitation was performed in order to better understand the physical factors influencing dynamic airway collapse. In this report, we shall summarize the work completed in each area, the details of which may be found in the appropriate annual reports.

PATENTED STUDIES

During high frequency low volume oscillatory ventilation (HFV), the tidal volumes used are small in comparison to those used in conventional mechanical ventilation. As a result, it has been assumed that the average alveolar pressures which prevail during high frequency ventilation will likely be lower than those which prevail during conventional mechanical

ventilation. It was this idea which accounted for many of the presumed benefits which could accrue from using high frequency ventilation. For example, it had been hypothesized that low alveolar pressures may reduce the frequency of pneumothorax or other types of barotrauma associated with mechanical ventilations. Second, the lower pressures in the thorax were thought to lead to minimal cardiovascular compromise during mechanical ventilation. These ideas, however, were based on the unproven concept that alveolar pressure and mean airway pressure would track each other during high frequency ventilation. Since the major purpose of this contract was to study interaction between pulmonary mechanics and gas exchange in patients undergoing high frequency oscillatory ventilation, our first experiment was to examine the difference between mean airway pressure and lung volume during high frequency ventilation in patients with respiratory insufficiency.

We first studied eight patients requiring mechanical ventilatory support for either neuromuscular or pulmonary disease. Each of these patients had required prolonged mechanical ventilatory support so their medical condition was otherwise stable. A high frequency ventilator consisting of a servo-controlled linear magnetic motor attached to a piston was used to generate small volume- high frequency oscillations. The tidal volumes delivered to the patient were measured with a specially calibrated pneumotachograph and the circuit was opened to a 10 liter weighted spirometer through a high impedance connector. This allowed the patient's functional residual capacity to increase or decrease at the pressure dictated by the spirometer weight. Lung volume was monitored with a respiratory inductance plethysmograph which estimated lung volume

based on the cross-sectional area of the thorax and abdomen. During each trial of high frequency ventilation, each subject received several large breaths of oxygen, and then was allowed to exhale passively until a stable lung volume was reached. The patient was then connected to the HFV circuit and the change in lung volume at constant mean airway pressure monitored during application of high frequency ventilation at a variety of tidal volumes and frequency.

Despite maintenance of a constant mean airway pressure, in seven out of eight subjects studied, mean lung volume increased. The increase in lung volume above functional residual capacity (FRC) was dramatic. As oscillatory frequency increased, lung volume rose progressively in seven subjects. In many subjects, the volume above FRC was as large as 500 ml. Further, at a given frequency of oscillation, the lung volume increased to a greater extent at higher oscillatory volumes than at lower oscillatory volumes. Importantly, the pressure swings measured at the airway opening during oscillation were symmetric around a mean pressure of 5 cm of water, even though lung volume increased. Thus, these data clearly demonstrated pulmonary hyperinflation during HFV and a dissociation between mean alveolar and mean airway pressure.

We then went on to examine the physiological mechanisms responsible for this dynamic hyperinflation. At this time, our studies were guided by cineradiographic bronchograms obtained by our group during high frequency ventilation in dogs. These data suggested that airway collapse may commonly occur during the application of high frequency ventilation. In order to determine whether dynamic airway collapse resulted in this

transient hyperinflation, we restudied four patients with chronic respiratory insufficiency. An apparatus similar to that used previously was employed, however a balanced high impedance bias flow was used rather than a weighted spirometer as a source of fresh gas. In these studies, gas exchange, measured as the CO_2 removed during a short trial of high frequency ventilation, was measured in addition to lung hyperinflation. Further, and most importantly, oscillations were applied at a low or high mean airway pressure.

We found that when a fixed oscillation volume, 100 or 50 ml, was applied at low mean airway pressure, dynamic hyperinflation occurred at the lowest frequency applied and increased with frequency such that over a 1 liter change in dynamic FRC was seen in two subjects. In contrast, when the mean airway pressure was raised (7-13 cm of water), a different dependence of dynamic hyperinflation on frequency was observed. Although the elevated mean airway opening pressure itself was associated with an elevated mean lung volume over resting FRC, there was no further increase in lung volume as frequency was raised, until the frequency reached some critical value (1.5-4 Hz). Above this critical frequency, lung volume did increase with frequency in a fashion parallel to that seen at the lower mean airway opening pressure. This dependence on applied frequency, tidal volume, and mean airway opening pressure, strongly suggested dynamic flow limitation as the mechanism responsible for hyperinflation.

To further test this hypothesis, additional experiments were performed in which flow volume curves were obtained in chronically intubated patients by applying a large negative pressure at the airway

opening while measuring volume and volume change using the respiratory inductance plethysmograph. From this manuever, the flow limitation envelope could be determined for each patient and compared to the volume of gas trapped during high frequency ventilation. We found that the flow rates achieved during high frequency ventilation exceeded those which we achieved during steady expiratory flow, but this likely is due to alterations of the area-transmural pressure relationship during steady and oscillatory flow.

We expressed our results using a model based on a bipolar junction transistor as a flow limiting element and developed electrical analogue circuits similar to the mechanical circuits which we felt prevailed during high frequency ventilation. Using this flow limiting data, our analogue models demonstrated similar dependencies of lung hyperinflation on frequency and tidal volume as we observed experimentally.

MODEL STUDIES

Simultaneous with the patient studies, work was being carried out at MIT to understand the basic fluid mechanics of gas transport during high frequency ventilation. The first problem that we attacked in these studies, was the distribution of pressure drop during sinusoidal mean flows in a rigid four generation network of uniform diameter symmetrically branching tubes. The rationale for this study was that the basic pressure flow relationships, during oscillatory flow at high frequencies, were not well appreciated. Therefore, experimentally derived generalized laws that could be used to predict pressure drop across either the entire lung or

individual airways over a wide range of oscillatory flow conditions were developed. To accomplish this, we used a methodology for decomposing the pressure signal measured at a number of stations during oscillation of the rigid lung-like network into a series of Fourier terms.

To acquire the data, measurements were made on a four generation, symetrically branching network. Each generation had an internal diameter of 1 cm and a length to diameter ratio of 3.5. The branching angle was uniformly 70°. Flow was excited at the trachea using sinusoidal oscillations produced by motor and a piston. At the alveolar end, each of the sixteen terminal branches was connected to a long piece of tygon tubing which was open to atmosphere. The pressure drop was then measured at a number of stations in the network while tidal volume and frequency were varied such that dynamic similarity would prevail to conditions under which HFV would be applied in the human lung.

The pressure difference between any two measurement locations in such a model can be influenced by three effects: instantaneous acceleration of the mass of fluid contained within the control volume between two stations, viscous dissipation due to friction, and changes in the dynamic head as the fluid passes between the parent and child vessels. Thus, our measurements were expressed in terms of an energy conservation equation for a control volume in order to determine each of these three terms to the best extent possible. In this analysis, we considered only the component of the Fourier pressure at the oscillation frequency and at its first harmonic, as the contribution of other frequencies to the total pressure signal was found to be small.

Experiments were conducted over a range of frequencies from 0.15-20.0 Hz and tidal volumes in the range of 3-77 ml. This corresponds to a range of Reynolds numbers between 50 and 30,000, and dimensionless frequencies between 1 and 15. We found that the results could be expressed in two major groups, those in which the ratio of Reynolds number to dimensionless frequency was greater than 200, and those in which this product was less than 200. The data fit the following general forms for these two areas:

$Re/\alpha < 200$

$$\Delta p_{fund}/\rho V^2/2 = (\frac{L}{d})(\frac{Re}{\alpha^2})^{-1}$$

$Re/\alpha > 200$

$$\Delta p_{fund}/\rho V^2/2 = (\frac{L}{d})(\frac{Re}{\alpha^2})^{-.4}$$

where ΔP_{fund} is equal to pressure loss at the fundamental frequency, ρ is gas density, V is volume flow rate, L is length, D is diameter, Re is Reynolds number, and α is dimensionless frequency.

These pressure losses were then compared with a total transpulmonary pressure drop determined in dog lungs reported by other investigators. We found good agreement between the results obtained in the hardware model and the physiologic experiments, suggesting that the airways and their pressure losses account for the major portion of total pulmonary resistance under the circumstance of high volume low frequency oscillation.

We then went on to study the relationship between oscillatory flow in such a network, and gas transport characteristics. To make these measurements, a steady flow of a trace gas was infused at a constant rate from the alveolar end of a network similar to that described previously. The tracer gas used was methane which could be measured noninvasively using an infared absorption technique by using a laser operating at 3.391 m. In these experiments, the concentration of tracer gas at a number of locations in the model was determined during the steady imposition of volume flow, of a very small amount, through the network. This allowed us to calculate the effective diffusion coefficients at various loci within the network.

Two series of experiments were conducted that roughly spanned the same range of parameters for which pressure measurements were made. We found that it was most convenient to cast the axial dispersion coefficients into one of two general expressions:

$$(D_{eff} - \mathcal{K})/ = \tilde{q}\, Pec^{\tilde{r}}\, \beta^{\tilde{s}}$$

and

$$D_{eff} = \mathcal{K} + q\, V_t^{\,r}\, f^{s}$$

where D_{eff} is effective diffusivity, $\mathcal{K}$ is equal to molecular diffusivity, PEC is equal to the Peclet number, β is dimensionless frequency based on gas diffusivity, and q, r, s, and $\tilde{q}$, $\tilde{r}$, $\tilde{s}$, are experimentally determined coefficients. The values for these coefficients are given in Table 1. The data demonstrate that tidal volume exerts a greater

influence than frequency of oscillation on gas transport. Further, our results show a significant dependence on frequency, suggesting that the effects of unsteadiness are important. Interesting, the data lie remarkably close to the results for oscillatory flow in a straight tube, but are universally higher. This suggests that the enhancement of axial transport can be attributed to one or more of the following mechanisms: increased cross-stream mixing, a less uniform axial velocity profile, or convective streaming.

At this time, it became clear that dynamic flow limitation was of substantial importance in our patient studies. Therefore, modelling efforts were turned toward better understanding the fluid dynamics of this situation. Our first task was to describe the area transmural pressure relationship which prevailed in an airway in order to proceed with definitive modelling studies. The research under which this so-called "tube-law" was supported by other sources and therefore will not be defined in this report. However, using this constituative relationship, a model was developed which considered the fundamental fluid dynamics of pressure losses during transitions from subcritical to critical, and to supercritical flow. This model was applied to airways with dimensions similar to those which prevail in the human lung. In this model, a general approach to steady flow and collapsible tubes was used. We found that solutions could be obtained which contained a smooth sub- to supercritical transition, followed by a shock-like decceleration to subcritical speed, an elastic jump. The location and the strength of the elastic jump provided solutions which matched downstream or mouth pressures with airway pressures. Flow was then modelled by assuming that

a forced expiration can be described by a series of quasi-steady states at progressively decreasing fixed lung volumes. This is justified by the fact that the characteristic time for a forced expiration is much larger than both the time required for a wave to propagate along the bronchial tree, and for a fluid particle to traverse the branching network. The dimensionless governing equation resulting from this model is given below:

$$\frac{d\alpha}{d\xi} = \frac{\alpha}{1-S^2}\left[\frac{S^2}{A_0}\frac{dA_0}{d\xi} - \frac{1}{\alpha}\frac{d\Pi_{alv}}{d\xi} - \frac{2S^2 f_T L}{\alpha D_0} - \frac{\Pi + \Pi_{alv}}{\alpha \Pi'}\frac{1}{K}\frac{dK}{d\xi}\right]$$

$$\frac{dS^2}{d\xi} = \frac{S^2}{1-S^2}\left[\frac{-2+(2-M)S^2}{A_0}\frac{dA_0}{d\xi} + \frac{M}{\alpha}\frac{d\Pi_{alv}}{d\xi} + \frac{2MS^2 f_T L}{\alpha D_0} + \right.$$

$$\left. + \left[M\frac{\Pi + \Pi_{avl}}{\alpha \Pi'} - (1-S^2)\right]\frac{1}{K}\frac{dK}{d\xi}\right]$$

Where $\Pi' = \partial \Pi / \partial \alpha$ and $M = \alpha \Pi'' / \Pi'$, S = Speed index (measured Speed / local wavespeed, α = Area ratio (local area / area at reference pressure (A_0)), ξ = dimensionless distance x / L, Π = local pressure (as indicated by subscript), D_0 and A_0 are reference diameters and areas, L = reference length, f_T = friction coefficient, and K = airway wall stiffness. This presentation highlights the separate effects associated with variations in rest area, variations in alveolar pressure, friction and variations in wall stiffness, each of which represent the first or the fourth terms in this expression. It can be seen that mathematical singularities appear when the speed index "S" is equal to 1, since the denominator on the right hand side of both expressions goes to 0. It has been shown that one of two situations can exist when the speed index is equal to 1. If the numerator passes through 0 at precisely the same point

at which the speed index is equal to 1, then a smooth and continuous transition from subcritical to supercritical speed is possible. This can occur in a variety of ways which are outlined in detail in the third year final report.

SUMMARY

Our patient experiments clearly demonstrated that high frequency oscillatory ventilation is accompanied by dynamic hyperinflation of the thorax. Further, our studies demonstrated, with reasonable surety, that the mechanism for this hyperinflation is in fact dynamic flow limitation. Our modelling studies demonstrated the physical basis for pressure loss during high frequency oscillatory ventilation, and we derived general empirical laws relating local flow with local gas transport in a lung-like network. Finally, because of the importannce of expiratory flow limitation in the physiological events observed, critical modelling of this process was carried out in which the character of flow near the flow limiting segment could be better quantified.

MILITARY SIGNIFICANCE

From this data, it appears clear that high frequency ventilation by itself would be an inappropriate method of combat casualty support for three reasons: 1) large volumes of gas are required to achieve efficient gas transport; 2) the pressure losses associated with this transport are great, therefore requiring high airway pressures; and 3) a marked dynamic hyperinflation takes place in normal lungs which would likely be

accentuated in diseased lungs. This hyperinflation could result in cardiovascular compromise in a patient in whom such compromise could be life-threatening.

Although high frequency oscillatory ventilation per se would likely not be of use to the individual soldier, methods of ventilation based on the information obtained during this contract period could possibly be of use. For example, one could utilize short bursts of high frequency ventilation which would be accompanied by transient pulmonary hyperinflation and deflation. This inflation and deflation would act like conventional ventilation thereby improving the amount of gas transported per unit of applied gas and would also result in minimal cardiovascular compromise in that HFV would only be applied for short periods of time. However, before this approach can be used, further information is needed about the characteristics of the hyperinflation in certain pathologic circumstances and the optimal wave-form for mixing between airway and alveolar gas.

Table 1. Data Correlations.

Coefficients are provided below for two general expressions:

$$(D_{eff} - \lambda)/\quad = \tilde{q}\, Pcc^{\tilde{r}}\, \beta^{\tilde{s}}$$

and

$$D_{eff} = \lambda + q\, V_t^{\,r}\, f^{s}$$

Generation	Frequency range	$\tilde{q}$	$\tilde{r}$	$\tilde{s}$	q	r	s	Mean % error [a]
1	f < 4	0.114	1.41	-0.981	0.549	1.41	0.915	19.2
1	f > 4	0.034	2.13	-2.47	0.305	2.13	0.891	6.91
1	all data	0.155	2.10	-2.02	0.214	2.10	1.09	16.8
2	all data	0.208	1.47	-1.26	0.913	1.47	0.840	36.2
1 and 2	all data	0.078	1.66	-1.45	0.508	1.66	0.940	31.5

(a) Computed from the expression $(\sum^{N} |D_{eff,i} - D_i|/D_i)/N$ where D_i is the correlation value, $D_{eff,i}$ is the corresponding data value, and N is the total number of data points in the correlation.

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List of Publications:

Rossing, T.H., J. Solway, A.F. Saari, N. Gavriely, A.S. Slutsky, J.L. Lehr, and J.M. Drazen. Influence of the Endotracheal Tube on CO_2 Transport during High-Frequency Ventilation. Am. Rev. Respir. Dis. 129:54-57, 1984.

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List of personnel at MIT

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List of Publications

Akhavan, R., and R.D. Kamm. Pressure excursions during oscillatory flow in a branching network of tubes. **J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.** 57(3): 665-673, 1984.

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